REMARKS:

A. Status of the Claims

Claims 1-9 were originally filed with the case. An Official Action rejecting all pending claims was mailed January 18, 2002. Claim 1 was amended to clarify the subject matter of the claims in a Response to Office Action filed on April 18, 2002. Thus, claims 1-9 were pending at the time of the present Action. No claims are amended, added or cancelled herein. Claims 1-9 remain pending. For the Examiner's convenience, a clean copy of all pending claims is attached hereto as Appendix A.

B. The Yaacobi Reference is Not Prior Art

The Action rejects claims 1-8 under 35 U.S.C. § 103(a) as being unpatentable over Yaacobi (U.S. Patent No. 6,416,777). Yaacobi is said to disclose "nepafenac for treating the eye topically including a tenon's capsule" (Action, page 2). The Action acknowledges that Yaacobi does not teach the use of nepafenac to treat angiogenesis *per se*, but asserts that the skilled artisan "would find ample motivation from [Yaacobi] to employ the compound Nepafenac against the specific eye diseases disclosed in [Yaacobi] with a reasonable expectation that said Nepafenac would be effective for combating said eye diseases" (Action, page 3, emphasis added).

While Applicants disagree that Yaacobi obviates the present invention, Applicants submit herewith a declaration under 37 C.F.R. § 1.131 to remove the Yaacobi reference from availability as prior art. The declaration provides documentary evidence that the inventors were in possession of the present invention prior to the publication of Yaacobi. Therefore, it is respectfully requested that the obviousness rejection based on Yaacobi be withdrawn.

C. The Claims are Patentable over Hellberg

The Action next rejects claims 1-8 under 35 U.S.C. § 103(a) as being unpatentable over Hellberg (U.S. Patent No. 6,342,524). Hellberg is said to teach the compounds of the invention for treating glaucoma. Although Hellberg mentions only GLC1A glaucoma, the Action takes the position that the skilled artisan would be motivated to employ the claimed compound against any form of glaucoma with a reasonable expectation of success. Applicants respectfully traverse.

The Action relies on the '524 patents teaching of the treatment of GLC1A glaucoma and the inclusion of "neovascular glaucoma" in the list of disorders to be treated by the present invention to support its position of obviousness. Unfortunately, the Action seems to disregard the remainder of the '524 patent for what it teaches regarding glaucoma and the use of non-steroidal anti-inflammatory agents in its treatment. The Action further seems to disregard the vast differences between GLC1A glaucoma and neovascular glaucoma. This amounts to a "picking and choosing" of certain parts of the reference while ignoring other aspects of it.

The Federal Circuit has held that "it is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference *fairly suggests* to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (CCPA 1965)). This principle holds true for the judicially created doctrine of obviousness-type double patenting as well.

The '524 patent goes on beyond its first sentence to discuss the relationship of the GLC1A gene to the occurrence of glaucoma. The GLC1A gene encodes a 57 kD protein that is expressed in the trabecular meshwork (TM) (col. 2, lines 20-21). The expression of this protein is upregulated by glucocorticoids (col. 2, lines 23-25). The glucocorticoid induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma. (col. 2, lines 32-35). It is this effect, the increase in ocular hypertension caused by glucocorticoid induction of the GLC1A protein, that the '524 patent seeks to treat.

The '524 patent discusses the mechanism by which the glucocorticoid induction of the GLC1A protein causes an increase in ocular hypertension, or intraocular pressure (IOP). It states, in pertinent part:

> It is known that the trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton [ ] and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, *the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises.* If this state of elevated intraocular pressure (IOP) is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field.

(col. 3, lines 16-37, *citations omitted, emphasis added*). The aim of the '524 patent is to decrease the IOP in glaucoma patients suffering from an increased IOP due to glucocorticoid induction of the expression of the GLC1A. The '524 patent does not discuss the administration of derivatives of 3-benzoylphenylacetic acid to treat neovascular glaucoma, much less to treat angiogenesis-related disorders. In fact, the '524 patent discusses the use of

such compounds only in combination with a prostaglandin for the treatment of GLC1A glaucoma. The '524 patent does not discuss the use of derivatives of 3-benzoylphenylacetic acid by themselves to treat angiogenesis-related disorders.

The purpose of the presence of non-steroidal cyclooxygenase inhibitors in the combinations of the '524 patent is to prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of the '524 patent provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, the focus of the '524 patent is to treat GLC1A glaucoma by lowering IOP, not to directly treat angiogenesis-related disorders.

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or

modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

The Action appears to be ignoring what the '524 patent *fairly suggests* to one skilled in the art." *Bausch & Lomb*, 230 U.S.P.Q. at 419. As discussed above, the '524 patent suggests to the skilled artisan that the administration of derivatives of 3-benzoylphenylacetic acid in combination with a prostaglandin will prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of the '524 patent provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, the focus of the '524 patent is to treat GLC1A glaucoma by lowering IOP.

Neovascular glaucoma, on the other hand, results from the development of new neovascularization, or new abnormal blood vessels, in the angle of the eye, which obstructs the outflow of fluid from the trabecular meshwork. Typcically, this neovascularization is treated using pan-retinal laser photocoagulation (PRP). Unfortunately, this laser ablation of the vessels is rarely effective and is generally only a temporary measure. (*See* http://www.eyemdlink.com/Condition.asp?ConditionID=298). Other current forms of therapy for neovascular glaucoma include glaucoma filtration surgery, implantation of a

glaucoma drainage device, and cyclocryotherapy. Clearly, these forms of treatment are rather invasive. Thus, prevention of neovascular glaucoma is of vital importance.

There is no suggestion or motivation within the '524 patent to administer the compounds of the present invention by themselves for the sole purpose of treating angiogenesis-related disorders. As explained above, the focus of the invention of the '524 patent is to lower IOP by administering a combination of compounds. The remainder of the description of the problem and the solution provided in the '524 patent focuses on the increase of ocular hypertension caused by glucocorticoid induction of the GLC1A protein. This is what the '524 patent seeks to treat.

In light of the foregoing arguments, Applicants respectfully submit that the double patenting rejection based on U.S. Patent No. 6,342,524 is overcome.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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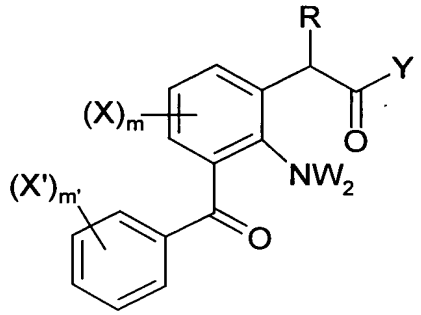
APPENDIX A – Pending Claims

1. (amended) A method of treating or preventing an angiogenesis-related disorder in a patient suffering from such a disorder which comprises administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or derivative of the formula:



wherein

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),

$-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_n2$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $—(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_n2R^4$, CF_3, R^4, NO_2;

R^4 = C_{1-6} (un)branched alkyl;

m = 0-3;

m' = 0-5; and

W = O, H.

2. The method of Claim 1 wherein

R = H, C_{1-2} alkyl;

Y = NR'R";

R' = H, C_{1-6} (un)branched alkyl, —$(CH_2)_n Z(CH_2)_{n'} A$;

Z = nothing, O, $CHOR^3$, NR^3;

R_3 = H;

A = H, OH, (un)substituted aryl (substitution as defined by X below);

X and X' independently = H, F, Cl, Br, CN, CF_3, OR', SR^4, R^4;

R" = H;

$R^4 = C_{1-4}$ (un)branched alkyl;

m = 0-2;

m' = 0-2;

W = H;

n = 2-4; and

n' = 0-3.

3. The method of Claim 2 wherein the 3-benzoylphenylacetic acid or derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. The method of Claim 1 wherein the angiogenesis-related disorder is an ophthalmic angiogenesis-related disorder.

5. The method of claim 4, wherein the 3-benzoylphenylacetic acid or derivative is topically administered to the eye.

6. The method of Claim 5 wherein the therapeutically effective amount of 3-benzoylphenylacetic acid or derivative is from about 0.001 to about 4.0% (w/v).

7. The method of Claim 4 wherein the angiogenesis-related disorder is selected from the group consisting of exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy; retinopathy of prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium.

8. The method of claim 1 wherein the 3-benzoylphenylacetic acid or derivative is administered orally, intravenously, in a subconjunctival injection or implant, in a sub-Tenon's injection or implant, in an intravitreal injection or implant, or in a surgical irrigating solution.

9. The method of claim 1 wherein the angiogenesis-related disorder is selected from the group consisting of prostate cancer; lung cancer; breast cancer; bladder cancer; renal cancer; colon cancer; gastric cancer; pancreatic cancer; ovarian cancer; melanoma; hepatoma; sarcoma; and lymphoma.